

# Direct Amination of Arenes with Azodicarboxylates Catalyzed by Bisulfate Salt/HFIP Association

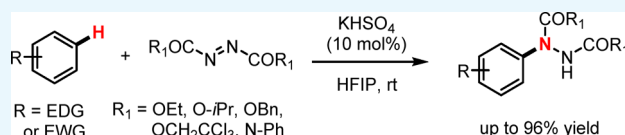
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## Supporting Information

**ABSTRACT:** A mild and efficient amination of arenes with azodicarboxylates using potassium bisulfate (KHSO<sub>4</sub>) as the catalyst in 1,1,1,3,3,3-hexafluoro-2-propanol has been developed. This protocol allowed the amination of a broad range of arenes leading to corresponding hydrazides in good to excellent yields.



## INTRODUCTION

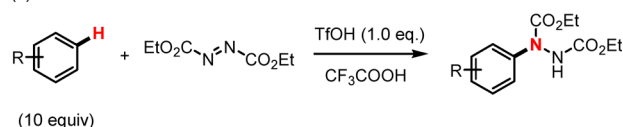
The development of efficient and novel methods creating the C—N bond on aromatics is always at the forefront of research in synthetic organic chemistry due to the omnipresence of arylamines in a variety of pharmaceuticals and natural products.<sup>1</sup> While many classical transformations have been established,<sup>2</sup> direct amination of aryl C—H bonds has been pursued as a more step-economical route. Important progress has been realized in the direct C—H amination of arenes to C—N bonds in the past decades,<sup>3</sup> but the requirement for a coordinating directing group limits the potential substrate scope. Therefore, the development of the C—H amination of arenes without the aid of directing groups increased in recent years.<sup>4</sup> Among them, electrophilic amination of simple arenes is one of the most useful protocols. Different amination systems using azodicarboxylates in the presence of Lewis acids or Brønsted acids have been developed in the past decades.<sup>5</sup> However, these reaction systems are efficient only to electron-rich arenes. In 2001, the Kim group described the first example of electrophilic amination of unactivated arenes (Scheme 1a).<sup>6</sup> However, conditions are very harsh, using a stoichiometric amount of super acid TfOH as the catalyst and trifluoroacetic acid as the solvent. The amination of electron-rich and electron-poor arenes with azodicarboxylates has been reported in the presence of metal catalysts (Scheme 1b).<sup>7</sup> Although effective, these reactions suffer from one or more disadvantages such as the use of sensitive and expensive metal catalysts (AuCl<sub>3</sub>, RuCl<sub>3</sub>). Furthermore, the poor reactivity of electron-poor arenes needs to use expensive electron-deficient bis(2,2,2-trichloroethyl)azodicarboxylate as the nitrogen source.

Considering previous results, we believe that it is still desirable to develop an efficient system for the direct amination of electron-rich and -poor arenes under mild conditions without a metal catalyst and with cheap reagents.

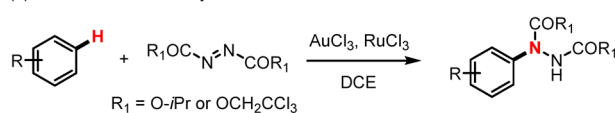
Fluorinated alcohols, particularly 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), have been shown to be beneficial as solvents, cosolvents, or additives in organic synthesis with a nearly unique set of properties (strong hydrogen-bond

## Scheme 1. Direct Amination of Simple Arenes Using Azodicarboxylates

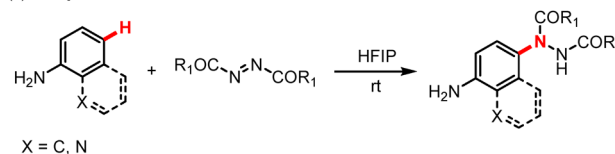
(a) Amination of unactivated arenes under harsh condition



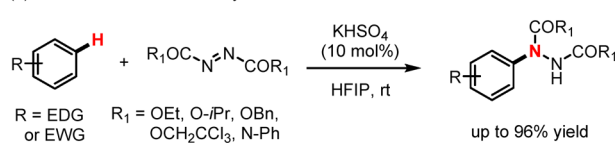
(b) Transition-metal catalyzed amination of unactivated arenes



(c) Our previous work: Amination of electron-rich aniline in HFIP



(d) This work: Acid salt catalyzed amination of unactivated arenes in HFIP



donating ability, high ionizing power, mild acidity, and low nucleophilicity).<sup>8</sup> Recently, the amination of anilines with azodicarboxylates in HFIP under mild conditions has been reported by our group (Scheme 1c).<sup>9</sup> Given the importance of the amination of aromatics, we sought to optimize conditions for aromatics of weak reactivity (Scheme 1d). We turned toward mild conditions that are easy to implement in the

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presence of weaker acid catalysts than TFA or TfOH because HFIP can further enhance their acidity by the hydrogen network.<sup>10</sup> We focused on cheap and available inorganic salt KHSO<sub>4</sub>, which showed its efficiency in the Friedel–Crafts benzylation reaction.<sup>11</sup>

## RESULTS AND DISCUSSION

We studied first the direct amination of *p*-xylene **1a** with diethyl azodicarboxylate (DEAD) **2a** as the model system (Table 1). We checked the reaction in HFIP without catalyst.

**Table 1. Optimization of the Reaction Conditions<sup>a</sup>**

entry	catalyst (10 mol %)	solvent	t (h)	yield of <b>3aa</b> (%) <sup>b</sup>
1		HFIP	16	26
2	KHSO <sub>4</sub>	HFIP	2	91
3	NaHSO <sub>4</sub>	HFIP	2	90
4	Na <sub>2</sub> SO <sub>4</sub>	HFIP	16	38
5	KHSO <sub>4</sub>	neat	16	0
6 <sup>c</sup>	KHSO <sub>4</sub>	HFIP	2	81 (12) <sup>d</sup>
7	KHSO <sub>4</sub>	TFE	16	trace
8	TFA	HFIP	16	32
9	TfOH	HFIP	5 min	94

<sup>a</sup>Conditions: **1a** (1.5 mmol, 3.0 equiv), **2a** (0.5 mmol, 1.0 equiv), and catalyst (10 mol %) were dissolved in solvent (2 mL) and stirred at r.t. for a specified period unless otherwise noted. <sup>b</sup>Isolated yield. <sup>c</sup>*p*-xylene (1.0 equiv) was used. <sup>d</sup>Isolated yield of bisaminated product (based on DEAD).

After 16 h, the product **3aa** was isolated in 26% yield (entry 1). To our satisfaction, 10 mol % KHSO<sub>4</sub> can improve the yield to 91% in only 2 h (entry 2). Using NaHSO<sub>4</sub> as the catalyst led to the same result (entry 3). A dramatic drop in yield to 38% was observed when Na<sub>2</sub>SO<sub>4</sub> is used instead of KHSO<sub>4</sub> (entry 4). This experiment shows the involvement of the OH function in the catalysis of the amination reaction. Potassium bisulfate is a green, cheap, and available inorganic salt that is a strong acid, the pK<sub>a</sub> is 1.9, and the acidity was further enhanced by the hydrogen network formed with HFIP. Indeed, when reaction was performed neat without HFIP, no reaction occurred (entry 5). In addition, when 1.0 equiv of *p*-xylene was used, 81% yield of product **3aa** with 12% of the bisaminated product was isolated (entry 6). Next, the effect of different solvents has been investigated. Unexpectedly, only a trace of the product was observed in TFE (entry 7). Other classical solvents such as EtOH, DCM, THF, H<sub>2</sub>O, CH<sub>3</sub>CN, and CH<sub>3</sub>NO<sub>2</sub> did not produce a detectable amount of product. Surprisingly, strong protic acid TFA (pK<sub>a</sub> −0.3) leads to a poor result (entry 8). Of course, the super acid TfOH (pK<sub>a</sub> −14.7), which is more expensive and less easy to handle, led to the product **3aa** (94%) in 5 min (entry 9).

The substrate scope of arenes has been examined with the optimized conditions (Table 1, entry 2). Results are reported in Table 2. Mesitylene, *o*-, and *m*-xylene were aminated to produce the corresponding aryl hydrazides **3ba–3da** in excellent yields with a single regioisomer. From the phenol, the corresponding aminated product **3ea** in favor of the *para* position (*p/o* ratio of 7.5:1) was isolated in 82% yield.

**Table 2. Amination of Different Arenes with DEAD<sup>a</sup>**

1b–1q	2a	3ba–3qa
 <b>3ba</b> , 16 h, 94 %	 <b>3ca</b> , 2 h, 92 %	 <b>3da</b> , 2 h, 95 %
 <b>3ea</b> , 0.5 h, 82% ( <i>p/o</i> : 7.5/1)	 <b>3fa</b> , 10 min, 96% ( <i>p/o</i> : 4.9/1) <sup>b</sup>	 <b>3ga</b> , 10 min, 85% ( <i>o/m</i> : 9.6/1)
 <b>3ha</b> , 2 h, 86% ( <i>mono/di</i> : 8.6/1)	 <b>3ia</b> , 2 h, 84% ( <i>p/o</i> : 7.2/1)	 <b>3ja</b> , 2 h, 75% ( <i>p/o</i> : 5.8/1)
 <b>3ka</b> , 2 h, 93%	 <b>3la</b> , 2 h, 95%	 <b>3ma</b> , 16 h, 89%
 <b>3na</b> , 48 h, 48% <sup>c</sup>	 <b>3oa</b> , 48 h, 46% <sup>c</sup>	 <b>3pa</b> , 48 h, 39% <sup>c</sup>
 <b>3qa</b> , 48 h, 25% <sup>c</sup>	 <b>3ra</b> , 48 h, 25% <sup>c</sup>	 <b>3sa</b> , 48 h, 25% <sup>c</sup>
R = CF <sub>3</sub> , NO <sub>2</sub> , CN trace		

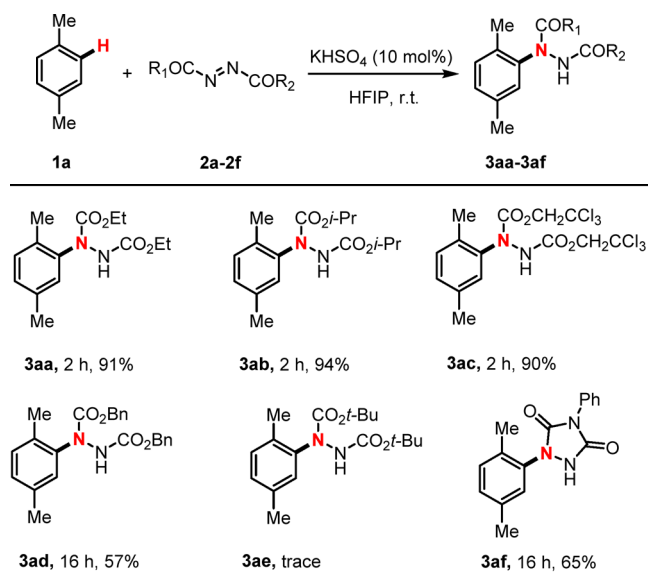
<sup>a</sup>Conditions: **1b–1q** (1.5 mmol, 3.0 equiv), **2a** (0.5 mmol, 1.0 equiv), and KHSO<sub>4</sub> (10 mol %) were dissolved in HFIP (2 mL) and stirred at r.t. for a specified period. Isolated yield. Ratios were determined by isolated yields of regioisomers. <sup>b</sup>Combined yield of regioisomers; ratio was determined by <sup>1</sup>H NMR. <sup>c</sup>1 equiv of catalyst was used.

Likewise, the amination of anisole to corresponding aminated product **3fa** (*p/o* ratio 4.9:1) resulted in 96% yield. The *para*-substituted anisole was aminated at the *ortho/meta* position (*o/m* ratio 9.6:1) (**3ga**). The amination of the toluene gave corresponding mono- (**3ha** isolated in 86% yield) and diamination products (*mono/di* ratio of 8.6:1). In addition, corresponding aminated derivatives **3ia** and **3ja** were obtained in good yields and a *para* selectivity. From naphthalene

derivatives **2k** and **2l**, the only corresponding aryl hydrazides **3ka** and **3la**<sup>12</sup> were isolated in 93 and 95% yields, respectively. For benzene, a 1,4-bisaminated product **3ma** was obtained as a single regioisomer. From electron-deficient arenes such as halobenzenes, reactions required 1 equiv of catalyst and 48 h to give moderate to low yields of corresponding aryl hydrazides **3na–3qa**.<sup>13</sup> The present KHSO<sub>4</sub>/HFIP system did not work with the electron-poor arenes such as benzonitrile, nitrobenzene, or benzonitrile.

Next, several azodicarboxylates with different ester substituents were subjected to the amination reaction under the standard conditions (Table 3). Diisopropyl and bis(2,2,2-

**Table 3.** Amination of *p*-Xylene with Different Azodicarboxylates<sup>a</sup>

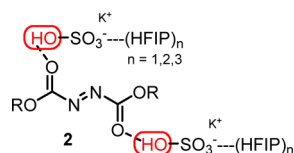


<sup>a</sup>Conditions: **1a** (1.5 mmol, 3.0 equiv), **2a–2f** (0.5 mmol, 1.0 equiv), and KHSO<sub>4</sub> (10 mol %) were dissolved in HFIP (2 mL) and stirred at r.t. for a specified period. Isolated yield.

trichloroethyl)azodicarboxylates **2b** and **2c** reacted smoothly with *p*-xylene **1a** to yield the corresponding aryl hydrazides **3ab** and **3ac** in excellent yields. The reaction of *p*-xylene **1a** with dibenzyl azodicarboxylate **2d** gave aminated product **3ad** in modest yield. For di-*t*-butyl azodicarboxylate **2e**, the corresponding aryl hydrazide **3ae** is present only in trace amounts because of its decomposition in the KHSO<sub>4</sub>/HFIP system.<sup>14</sup> With 4-phenyl-1,2,4-triazoline-3,5-dione **2f**, the reaction worked to afford the corresponding aryl hydrazide **3af** in 65% yield.

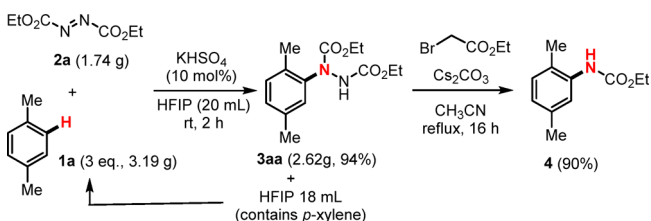
The association of KHSO<sub>4</sub> with HFIP leads to a strong organocatalyst that acts as an excellent H-bond donor and activates the carbonyl group of the DEAD **2**, increasing its electrophilicity (Scheme 2).

**Scheme 2.** Increased Electrophilicity of **2**



To demonstrate the utility of this protocol, the reaction was performed on a gram scale (Scheme 3). The reaction of *p*-

**Scheme 3.** Gram Scale and Deprotection Reaction



xylene **1a** with DEAD **2a** proceeded mildly in 2 h to afford the corresponding aryl hydrazide **3aa** in 94% yield. HFIP, which was previously recovered containing *p*-xylene, can be reused. In addition, the hydrazine **3aa** can be cleaved using the methyl bromoacetate/Cs<sub>2</sub>CO<sub>3</sub> system<sup>15</sup> and converted to amine **4** in 90% yield.

## CONCLUSIONS

In conclusion, we have developed a very efficient and mild amination reaction of arenes with azodicarboxylates by using a catalytic amount of KHSO<sub>4</sub> in HFIP. This process led to a broad range of arenes, including electron-poor arenes. Additional advantages of KHSO<sub>4</sub> are its low cost, ready availability, and easy removal in an aqueous workup. From this new efficient system, other applications are currently underway in our laboratory.

## EXPERIMENTAL SECTION

**General Information.** Thin-layer chromatography (TLC) was performed on silica gel 60F-250 (0.26 mm thickness) plates. The plates were visualized with UV light (254 nm) or with a 3.5% solution of phosphomolybdic acid in ethanol or with a solution of KMnO<sub>4</sub> in water. High-resolution mass spectra (HRMS) were obtained from Waters LCT Premier (ESI/TOF). Flash chromatography (FC) was performed on Merck 60 silica gel (230–400 mesh). Melting points were determined on a Kofler melting point apparatus. NMR spectra were measured on an Ultra field AVANCE 300 (<sup>1</sup>H, 300 MHz; <sup>13</sup>C, 75 MHz) spectrometer. Unless otherwise stated, NMR data were obtained under ambient temperature conditions. Chemical shifts for <sup>1</sup>H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard (dimethyl sulfoxide: δ 2.50 ppm, chloroform: δ 7.26 ppm, methanol: δ 3.31 ppm). Chemical shifts for <sup>13</sup>C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard (dimethyl sulfoxide: δ 39.52 ppm, chloroform: δ 77.16 ppm, methanol: δ 49.00 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, appt = apparent triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration.

**Reagents.** Unless otherwise noted, all commercial materials were purchased from various commercial sources (Sigma-Aldrich, Alfa Aesar, FluoroChem) and used as received without further purification. HFIP was provided by Central Glass Co. Ltd.

**General Procedures for Amination of Arenes with Azodicarboxylates.** To a stirred solution of arenes **1** (1.5



mmol, 3 equiv) and azodicarboxylates **2** (0.5 mmol, 1 equiv) in HFIP (2 mL) was added KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) under air. The reaction mixture was stirred at r.t. for 0.5–16 h. After that, the reaction mixture was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel using cyclohexane/ethyl acetate as the eluent to afford aryl hydrazides **3**.

Physical data of **3aa–3qa** and **3ab–3af** are presented.

**Diethyl 1-(2,5-Dimethylphenyl)hydrazine-1,2-dicarboxylate (3aa).**<sup>6</sup> The title compound was prepared between *p*-xylene (159.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 2 h and purified by using 25% EtOAc in cyclohexane as a white solid (128 mg, 91%).

M.p. 114–116 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 10.0 (s, 0.87 × 1H) and 9.96 (s, 0.23 × 1H), 7.17 (s, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 4.11–4.04 (m, 4H), 2.25 (s, 3H), 2.20 (s, 3H), 1.21–1.10 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 156.1, 154.5, 140.7, 135.6, 132.1, 130.2, 128.4, 127.4, 61.8, 60.8, 20.4, 16.9, 14.4; HRMS calcd for C<sub>14</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub> [M + H]<sup>+</sup> *m/z* 281.1501, found 281.1497.

**Diethyl 1-(3,4-Dimethylphenyl)hydrazine-1,2-dicarboxylate (3ba).**<sup>5d</sup> The title compound was prepared between *o*-xylene (159.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 16 h and purified by using 25% EtOAc in cyclohexane as a white solid (132 mg, 94%).

M.p. 68–70 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 9.95 (s, 0.80 × 1H), 9.58 (0.20 × 1H), 7.12–7.04 (m, 3H), 4.15–4.05 (m, 4H), 2.19 (s, 3H), 2.19 (s, 3H), 1.22–1.15 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 155.9, 154.3, 139.8, 136.2, 133.8, 129.4, 124.7, 121.2, 61.9, 60.9, 19.5, 18.8, 14.5, 14.4; HRMS calcd for C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>Na [M + Na]<sup>+</sup> *m/z* 303.1321, found 303.1314.

**Diethyl 1-(2,4-Dimethylphenyl)hydrazine-1,2-dicarboxylate (3ca).**<sup>16</sup> The title compound was prepared between *m*-xylene (159.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t.] for 2 h and purified by using 25% EtOAc in cyclohexane as a white solid (130 mg, 93%).

M.p. 96–98 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 9.99 and 9.94 (2 × s, 0.82 × 1H), 9.65 (s, 0.20 × 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.03–6.98 (m, 2H), 4.10–4.03 (m, 4H), 2.25 (s, 3H), 2.20 (2, 3H), 1.20–1.08 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 156.1, 154.6, 138.4, 137.1, 135.0, 130.9, 128.3, 127.0, 126.9, 61.8, 60.8, 20.5, 17.2, 14.4; HRMS calcd for C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>O<sub>4</sub>Na [M + Na]<sup>+</sup> *m/z* 303.1321, found 303.1320.

**Diethyl 1-Mesitylhydrazine-1,2-dicarboxylate (3da).**<sup>16</sup> The title compound was prepared between mesitylene (180.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 2 h and purified by using 25% EtOAc in cyclohexane as a white solid (140 mg, 95%).

M.p. 162–164 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 9.82 (s, 0.40 × 1H) and 9.76 (s, 0.60 × 1H), 6.85 (s, 2H), 4.15–4.02 (m, 4H), 2.23 (s, 6H), 2.21 (s, 3H), 1.24–1.05 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 156.2, 155.9, 154.8, 154.2, 136.9, 136.9, 136.5, 136.1, 135.7, 128.9, 61.9, 60.7, 20.4, 18.0, 14.5; HRMS calcd for C<sub>15</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>Na [M + Na]<sup>+</sup> *m/z* 317.1477, found 317.1501.

**Diethyl 1-(4-Hydroxyphenyl)hydrazine-1,2-dicarboxylate (3ea).**<sup>5d</sup> The title compound was prepared between phenol (141.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and

KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 0.5 and purified by using 50% EtOAc in cyclohexane as a white solid (110 mg, 82%).

M.p. 148–150 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 9.91 (s, 1H), 9.50 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 2H), 4.12–4.03 (m, 4H), 1.20–1.13 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 156.0, 155.8, 154.7, 133.7, 126.0, 115.0, 61.9, 60.9, 14.5, 14.4; HRMS calcd for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub>Na [M + Na]<sup>+</sup> *m/z* 291.0957, found 291.0954.

**Diethyl 1-(4-Methoxyphenyl)hydrazine-1,2-dicarboxylate and Diethyl 1-(2-Methoxyphenyl)hydrazine-1,2-dicarboxylate (4:9:1) (3fa).**<sup>16</sup> The title compound was prepared between anisole (162.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 10 min and purified by using 30% EtOAc in cyclohexane as a colorless oil (135 mg, 96%).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 9.94 (s, 0.84 × 1H), 9.57 (s, 0.16 × 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 0.16 × 2H), 6.91 (d, *J* = 8.8 Hz, 0.84 × 1H), 4.14–4.04 (m, 4H), 3.77 (s, 0.16 × 3H), 3.74 (s, 0.84 × 3H), 1.21–1.14 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 157.3, 155.9, 154.5, 135.1, 128.9, 128.0, 125.7, 120.2, 113.7, 112.2, 61.9, 61.7, 60.9, 60.8, 55.5, 55.3, 14.4, 14.4; HRMS calcd for C<sub>13</sub>H<sub>19</sub>N<sub>2</sub>O<sub>5</sub> [M + H]<sup>+</sup> *m/z* 283.1294, found 283.1289.

**Diethyl 1-(5-Chloro-2-methoxyphenyl)hydrazine-1,2-dicarboxylate (3ga).** The title compound was prepared between 4-chloroanisole (214.5 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 10 min and purified by using 30% EtOAc in cyclohexane as a white solid (134 mg, 85%).

M.p. 110–112 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 9.98 (s, 0.83 × 1H) and 9.57 (s, 0.17 × 1H), 7.34 (bs, 2H), 7.11 (d, *J* = 8.1 Hz, 1H), 4.09–4.07 (m, 4H), 3.79 (s, 3H), 1.20–1.13 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 156.3, 154.4, 153.4, 131.6, 128.6, 127.5, 123.2, 113.9, 62.0, 61.0, 56.0, 14.4, 14.3; HRMS calcd for C<sub>13</sub>H<sub>17</sub>N<sub>2</sub>O<sub>5</sub>NaCl [M + Na]<sup>+</sup> *m/z* 339.0724, found 339.0712.

**Diethyl 1-(*p*-Tolyl)hydrazine-1,2-dicarboxylate (3ha).**<sup>16</sup> The title compound was prepared between toluene (138.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 2 h and purified by using 25% EtOAc in cyclohexane as a colorless oil (115 mg, 86%).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 9.97 (s, 0.81 × 1H) and 9.61 (s, 0.19 × 1H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 4.16–4.05 (m, 4H), 2.28 (s, 3H), 1.22–1.16 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 155.9, 154.3, 139.6, 135.0, 128.9, 123.6, 62.0, 60.9, 20.4, 14.4, 14.3; HRMS calcd for C<sub>13</sub>H<sub>19</sub>N<sub>2</sub>O<sub>4</sub> [M + H]<sup>+</sup> *m/z* 267.1345, found 267.1340.

**Diethyl 1-(4-(*tert*-Butyl)phenyl)hydrazine-1,2-dicarboxylate (3ia).** The title compound was prepared between *tert*-butylbenzene (201.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 2 h and purified by using 25% EtOAc in cyclohexane as a colorless oil (130 mg, 84%).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 9.99 (s, 0.78 × 1H) and 9.60 (s, 0.22 × 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 4.17–4.05 (m, 4H), 1.27 (s, 9H), 1.22–1.16 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 155.9, 154.3, 148.0, 139.5, 125.2, 123.1, 62.0, 60.9, 34.1, 31.1, 14.5, 14.3; HRMS calcd for C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>Na [M + Na]<sup>+</sup> *m/z* 331.1634, found 331.1626.

**Diethyl 1-(4-Isobutylphenyl)hydrazine-1,2-dicarboxylate (3ja).** The title compound was prepared between isobutylbenzene (201.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 2 h and purified by using 25% EtOAc in cyclohexane as a colorless oil (115 mg, 75%).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 9.98 (s, 0.80 × 1H) and 9.60 (s, 0.20 × 1H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 4.16–4.06 (m, 4H), 2.42 (d, *J* = 7.1 Hz, 2H), 1.86–1.77 (m, 1H), 1.22–1.13 (m, 6H), 0.87 (s, 3H), 0.85 (s, 3H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 156.0, 154.3, 139.8, 138.6, 128.9, 123.2, 62.0, 60.9, 44.0, 29.6, 22.1, 14.5, 14.3; HRMS calcd for C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>Na [M + Na]<sup>+</sup> *m/z* 331.1634, found 331.1630.

**Diethyl 1-(Naphthalen-1-yl)hydrazine-1,2-dicarboxylate (3ka).**<sup>5d</sup> The title compound was prepared between naphthalene (192.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 2 h and purified by using 25% EtOAc in cyclohexane as a white solid (140 mg, 93%).

M.p. 148–150 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 10.22 (s, 0.79 × 1H) and 9.90 (s, 0.21 × 1H), 8.10 (bs, 1H), 7.98–7.91 (m, 2H), 7.63–7.52 (m, 4H), 4.12–4.05 (m, 4H), 1.20–0.98 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 156.3, 155.2, 138.3, 133.9, 129.7, 128.3, 128.0, 126.5, 126.3, 125.7, 125.4, 123.2, 62.1, 61.0, 14.5, 14.4; HRMS calcd for C<sub>16</sub>H<sub>19</sub>N<sub>2</sub>O<sub>4</sub> [M + H]<sup>+</sup> *m/z* 303.1345, found 303.1351.

**Diethyl 1-(1-Methylnaphthalen-2-yl)hydrazine-1,2-dicarboxylate (3la).** The title compound was prepared between 1-methylnaphthalene (213.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 2 h and purified by using 25% EtOAc in cyclohexane as a white solid (150 mg, 95%).

M.p. 156–158 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 10.17 (s, 0.79 × 1H) and 9.85 (s, 0.21 × 1H), 8.13 (bs, 1H), 8.05–8.05 (m, 1H), 7.60–7.52 (m, 3H), 7.38 (d, *J* = 7.5 Hz, 1H), 4.12–4.05 (m, 4H), 2.65 (s, 3H), 1.20–0.98 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 156.2, 155.3, 136.7, 134.7, 132.6, 129.7, 126.1, 125.0, 124.4, 123.7, 61.9, 60.9, 19.0, 14.4, 14.4; HRMS calcd for C<sub>17</sub>H<sub>21</sub>N<sub>2</sub>O<sub>4</sub> [M + H]<sup>+</sup> *m/z* 317.1501, found 317.1496.

**Tetraethyl 1,1'-(1,4-Phenylene)bis(hydrazine-1,2-dicarboxylate) (3ma).** The title compound was prepared between benzene (117.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 16 h and purified by using 25% EtOAc in cyclohexane as a white solid (95 mg, 89%).

M.p. 182–184 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 10.03 (s, 0.81 × 1H) and 9.65 (s, 0.19 × 1H), 7.33 (s, 2H), 4.18–4.06 (m, 4H), 1.23–1.14 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 155.9, 154.2, 139.4, 123.5, 62.2, 61.1, 14.4, 14.3; HRMS calcd for C<sub>18</sub>H<sub>30</sub>N<sub>5</sub>O<sub>8</sub> [M + NH<sub>4</sub>]<sup>+</sup> *m/z* 444.2094, found 444.2086.

**Diethyl 1-(4-Fluorophenyl)hydrazine-1,2-dicarboxylate (3na).** The title compound was prepared between fluorobenzene (144.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.5 mmol, 1.0 equiv) in HFIP (2 mL) at r.t. for 48 h and purified by using 25% EtOAc in cyclohexane as a colorless oil (65 mg, 48%).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 10.03 (s, 0.82 × 1H) and 9.65 (s, 0.18 × 1H), 7.40–7.35 (m, 2H), 7.23–7.16 (m, 2H), 4.17–4.06 (m, 4H), 1.22–1.16 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 161.2 (d, *J* = 241.5 Hz), 156.0, 154.2, 138.4,

125.8, 115.3 (d, *J* = 23.25 Hz), 62.2, 61.1, 14.4, 14.3; HRMS calcd for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>F [M + H]<sup>+</sup> *m/z* 271.1094, found 271.1098.

**Diethyl 1-(4-Chlorophenyl)hydrazine-1,2-dicarboxylate (3oa).**<sup>6</sup> The title compound was prepared between chlorobenzene (168.8 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.5 mmol, 1.0 equiv) in HFIP (2 mL) at r.t. for 48 h and purified by using 25% EtOAc in cyclohexane as a white solid (66 mg, 46%).

M.p. 72–74 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 10.07 (s, 0.80 × 1H) and 9.69 (s, 0.20 × 1H), 7.44–7.36 (m, 4H), 4.19–4.07 (m, 4H), 1.23–1.17 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 156.0, 154.0, 141.0, 129.6, 128.5, 124.6, 62.3, 61.1, 14.4, 14.2; HRMS calcd for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>Cl [M + H]<sup>+</sup> *m/z* 287.0799, found 287.0796.

**Diethyl 1-(4-Bromophenyl)hydrazine-1,2-dicarboxylate (3pa).**<sup>17</sup> The title compound was prepared between bromobenzene (235.5 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.5 mmol, 1.0 equiv) in HFIP (2 mL) at r.t. for 48 h and purified by using 25% EtOAc in cyclohexane as a white solid (65 mg, 39%).

M.p. 70–72 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 10.07 (s, 0.81 × 1H) and 9.69 (s, 0.19 × 1H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 4.19–4.07 (m, 4H), 1.23–1.17 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 155.9, 153.9, 141.4, 131.4, 124.9, 117.7, 62.4, 61.2, 14.4, 14.3; HRMS calcd for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>Br [M + H]<sup>+</sup> *m/z* 331.0293, found 331.0298.

**Diethyl 1-(4-Iodophenyl)hydrazine-1,2-dicarboxylate (3qa).** The title compound was prepared between iodobenzene (306.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.5 mmol, 1.0 equiv) in HFIP (2 mL) at r.t. for 48 h and purified by using 25% EtOAc in cyclohexane as a white solid (47 mg, 25%).

M.p. 76–78 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 10.05 (s, 0.80 × 1H) and 9.67 (s, 0.20 × 1H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 4.19–4.07 (m, 4H), 1.23–1.09 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 155.9, 153.9, 141.9, 137.3, 125.0, 90.1, 62.3, 61.1, 14.4, 14.2; HRMS calcd for C<sub>12</sub>H<sub>15</sub>N<sub>2</sub>O<sub>4</sub>NaI [M + Na]<sup>+</sup> *m/z* 400.9974, found 400.9970.

**Diisopropyl 1-(2,5-Dimethylphenyl)hydrazine-1,2-dicarboxylate (3ab).**<sup>18</sup> The title compound was prepared between *p*-xylene (159.0 mg, 1.5 mmol), diisopropyl azodicarboxylate (101.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 2 h and purified by using 25% EtOAc in cyclohexane as a white solid (145 mg, 94%).

M.p. 106–108 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 9.86 (s, 0.76 × 1H) and 9.57 (s, 0.24 × 1H), 7.16 (s, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 4.86–4.80 (m, 2H), 2.24 (s, 3H), 2.19 (s, 3H), 1.21–1.10 (m, 12H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 155.8, 154.2, 153.8, 140.8, 135.4, 132.0, 130.1, 128.2, 127.4, 69.5, 69.2, 68.3, 21.8, 20.4, 16.9; HRMS calcd for C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>Na [M + Na]<sup>+</sup> *m/z* 331.1634, found 331.1629.

**Bis(2,2,2-trichloroethyl) 1-(2,5-Dimethylphenyl)hydrazine-1,2-dicarboxylate (3ac).** The title compound was prepared between *p*-xylene (159.0 mg, 1.5 mmol), bis(2,2,2-trichloroethyl) azodicarboxylates (190.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 2 h and purified by using 25% EtOAc in cyclohexane as a colorless oil (218 mg, 90%).

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 10.95 (s, 0.47 × 1H), 10.84 (s, 0.38 × 1H), 10.49 (s, 0.08 × 1H) and 10.38 (s, 0.07

× 1H), 7.41–7.03 (m, 3H), 4.95 (s, 2H), 4.93 (s, 2H), 2.31–2.26 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 154.4, 154.2, 153.3, 153.2, 139.4, 137.9, 137.8, 135.3, 132.4, 131.1, 130.4, 129.2, 129.0, 128.0, 127.4, 127.1, 126.6, 95.5, 95.3, 74.7, 74.0, 74.0, 20.6, 20.4, 17.2, 16.9; HRMS calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>Na<sub>3</sub>Cl<sub>3</sub>37Cl [M + Na]<sup>+</sup> *m/z* 508.8953, found 508.8943.

**Dibenzyl 1-(2,5-Dimethylphenyl)hydrazine-1,2-dicarboxylate (3ad).** The title compound was prepared between *p*-xylene (159.0 mg, 1.5 mmol), dibenzyl azodicarboxylate (149.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 16 h and purified by using 25% EtOAc in cyclohexane as a white solid (115 mg, 57%).

M.p. 110–112 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 10.3 (s, 0.38 × 1H), 10.2 (s, 0.40 × 1H), 9.94 (s, 0.12 × 1H), 9.86 (s, 0.10 × 1H), 7.33–7.04 (m, 13H), 5.12 (m, 4H), 2.24–2.08 (m, 6H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 156.0, 154.6, 154.1, 140.5, 136.2, 135.7, 132.1, 130.3, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.4, 127.2, 67.2, 66.3, 20.4, 16.9; HRMS calcd for C<sub>24</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>Na [M + Na]<sup>+</sup> *m/z* 427.1634, found 427.1638.

**1-(2,5-Dimethylphenyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (3af).** The title compound was prepared between *p*-xylene (159.0 mg, 1.5 mmol), 4-phenyl-1,2,4-triazoline-3,5-dione (83.0 mg, 0.5 mmol), and KHSO<sub>4</sub> (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 mL) at r.t. for 16 h and purified by using 25% EtOAc in cyclohexane as a white solid (88 mg, 65%).

M.p. 218–220 °C; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 11.30 (s, 1H), 7.54–7.43 (m, 5H), 7.33 (s, 1H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 2.32 (s, 3H), 2.30 (s, 3H); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 152.2, 150.3, 136.2, 134.9, 132.5, 131.7, 130.8, 129.4, 128.9, 127.9, 126.8, 126.3, 20.3, 17.2; HRMS calcd for C<sub>16</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup> *m/z* 282.1243, found 282.1249.

**Gram Scale Reaction.** To a stirred solution of *p*-xylene **1a** (30 mmol, 3.19 g) and DEAD **2a** (10 mmol, 1.74 g) in HFIP (20 mL) was added KHSO<sub>4</sub> (136 mg, 1.0 mmol) in air. The reaction mixture was stirred at r.t. for 2 h. After that, the mixture was filtered to remove KHSO<sub>4</sub>. Then, the HFIP solvent was recovered directly by atmospheric distillation from the reaction mixture (18 mL, contains *p*-xylene). The residue was purified by column chromatography on silica gel using cyclohexane/ethyl acetate (3:1) as the eluent to give **3aa** as a white solid (2.62, 94%).

**Deprotection Reaction.** To a stirred solution of **3aa** (0.5 mmol, 140 mg) and Cs<sub>2</sub>CO<sub>3</sub> (2.0 mmol, 652 mg) in CH<sub>3</sub>CN (2 mL) was added methyl bromoacetate (1.0 mmol, 167 mg), and the mixture was refluxed for 16 h. After that, the mixture was quenched with saturated NH<sub>4</sub>Cl and extracted with DCM. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and filtered. The mixture was evaporated under reduced pressure, and the crude product was purified by column chromatography on silica gel using cyclohexane/ethyl acetate (10:1) as the eluent to give **4** as a white solid (87 mg, 90%).

M.p. 98–100 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.63 (s, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.34 (s, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.32 (s, 3H), 2.21 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 154.1, 136.7, 135.8, 131.2, 130.3, 124.9, 121.8, 61.3, 21.3, 17.3, 14.7; HRMS calcd for C<sub>11</sub>H<sub>15</sub>NO<sub>2</sub>Na [M + Na]<sup>+</sup> *m/z* 216.1002, found 216.1000.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b00781.

Copies of the <sup>1</sup>H and <sup>13</sup>C NMR spectra (PDF)

Crystallographic data for **3la** (CIF)

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### Notes

The authors declare no competing financial interest.

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